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Naltrexone: A Possible Treatment for Prolonged Grief Disorder

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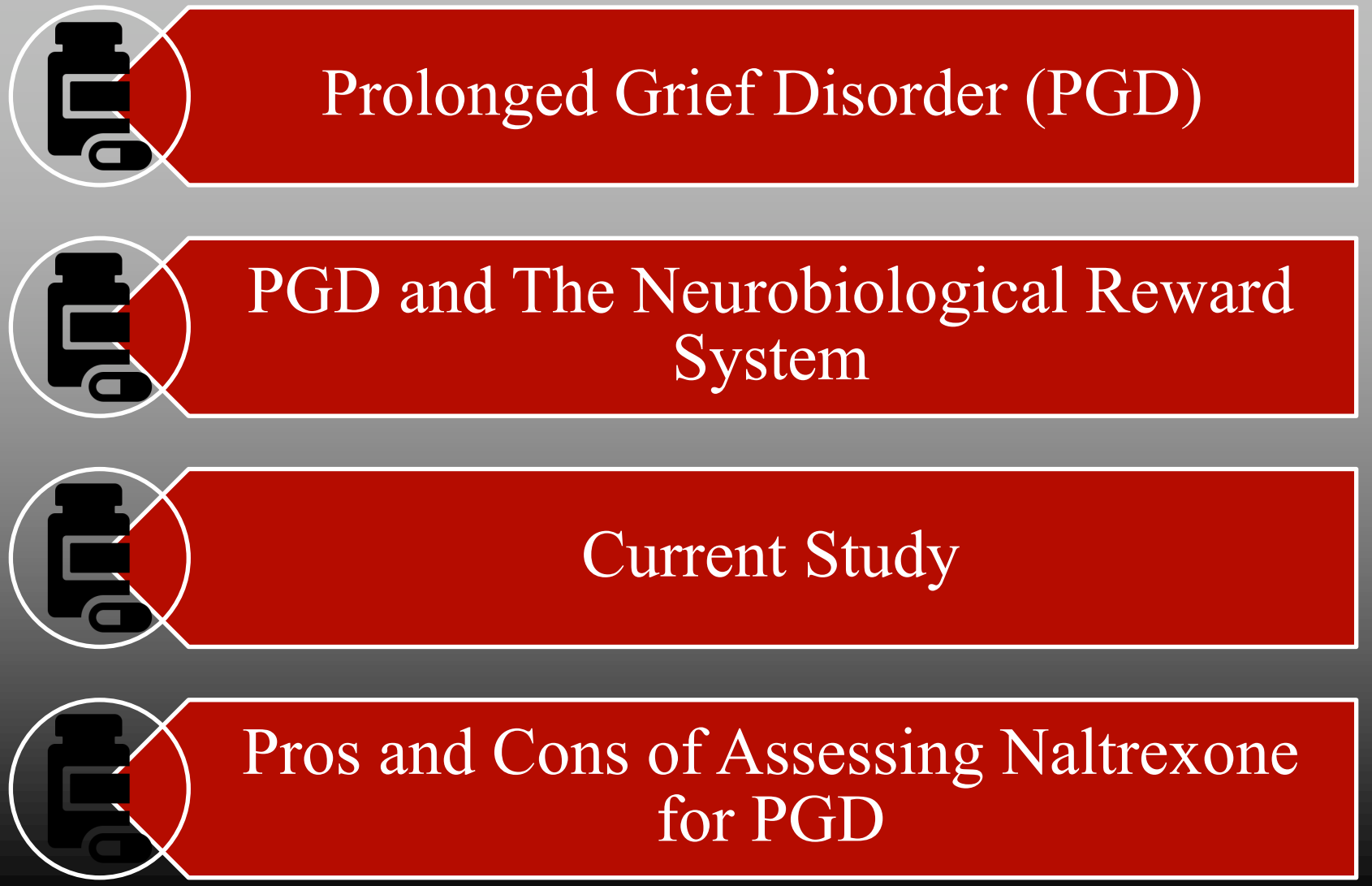
Disclosures

No Disclosures

Road Map


Prolonged Grief Disorder (PGD)
PGD and The Neurobiological Reward System
Current Study
Pros and Cons of Assessing Naltrexone for PGD

Prolonged Grief Disorder: DSM-5-TR

A. Death occurred at least 12 months ago

B. Nearly every day in the last month clinically significant degree of yearning and/or preoccupation

C. Identity disruption; disbelief; avoidance of reminders of the death; intense emotional pain; emotional numbness; meaninglessness; loneliness (need at least 3)

D. Impairment

Table 1 DSM-5-TR criteria for prolonged grief disorder

A. The death, at least 12 months ago, of a person who was close to the bereaved (for children and adolescents, at least 6 months ago).

B. Since the death, there has been a grief response characterized by one or both of the following, to a clinically significant degree, nearly every day or more often for at least the last month:
1. Intense yearning/longing for the deceased person
2. Preoccupation with thoughts or memories of the deceased person (in children and adolescents, preoccupation may focus on the circumstances of the death)

C. As a result of the death, at least 3 of the following 8 symptoms have been experienced to a clinically significant degree since the death, including nearly every day or more often for at least the last month:
1. Identity disruption (e.g., feeling as though part of oneself has died)
2. Marked sense of disbelief about the death
3. Avoidance of reminders that the person is dead (in children and adolescents, may be characterized by efforts to avoid reminders)
4. Intense emotional pain (e.g., anger, bitterness, sorrow) related to the death
5. Difficulty with reintegration into life after the death (e.g., problems engaging with friends, pursuing interests, planning for the future)
6. Emotional numbness (i.e., absence or marked reduction in the intensity of emotion, feeling stunned) as a result of the death
7. Feeling that life is meaningless as a result of the death
8. Intense loneliness (i.e., feeling alone or detached from others) as a result of the death

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The duration and severity of the bereavement reaction clearly exceeds expected social, cultural, or religious norms for the individual's culture and context.

F. The symptoms are not better explained by major depressive disorder, posttraumatic stress disorder, or another mental disorder, or attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Prolonged Grief Disorder: ICD-11

Criterion A. **Loss of an attachment figure**

Criterion B. **Separation Anxiety/Reactivity/re-experiencing**

- Constant longing, yearning or pining for the lost person;
- Intense feelings of emotional pain, sorrow, or pangs of grief related to the lost relationship
- Intrusive thoughts about the deceased

Criterion C. **Specific Social/Emotional dysfunction**

- Avoidance of reminders of the deceased
- Feeling stunned, shocked, or dazed by the loss
- Confusion about role in life or a diminished sense of self
- Trouble accepting the loss
- Difficulty trusting others since the loss
- Feelings of bitterness and anger over the loss
- Difficulty moving on
- Feeling emotionally numb since the loss
- Feeling that life is unfulfilling, empty, or meaningless without the decease

- Symptoms present for at least **6+ months**
- **Symptom-related reduction in functioning** (social, occupational, or other important areas)

Psychotherapy for PGD

- PROLONGED EXPOSURE AND COGNITIVE RESTRUCTURING
- BEHAVIORAL ACTIVATION
- PROLONGED GRIEF DISORDER THERAPY

SSRIs for Prolonged Grief Disorder?

- Few benefits with multiple side effects

- Best effects when coupled with psychotherapy

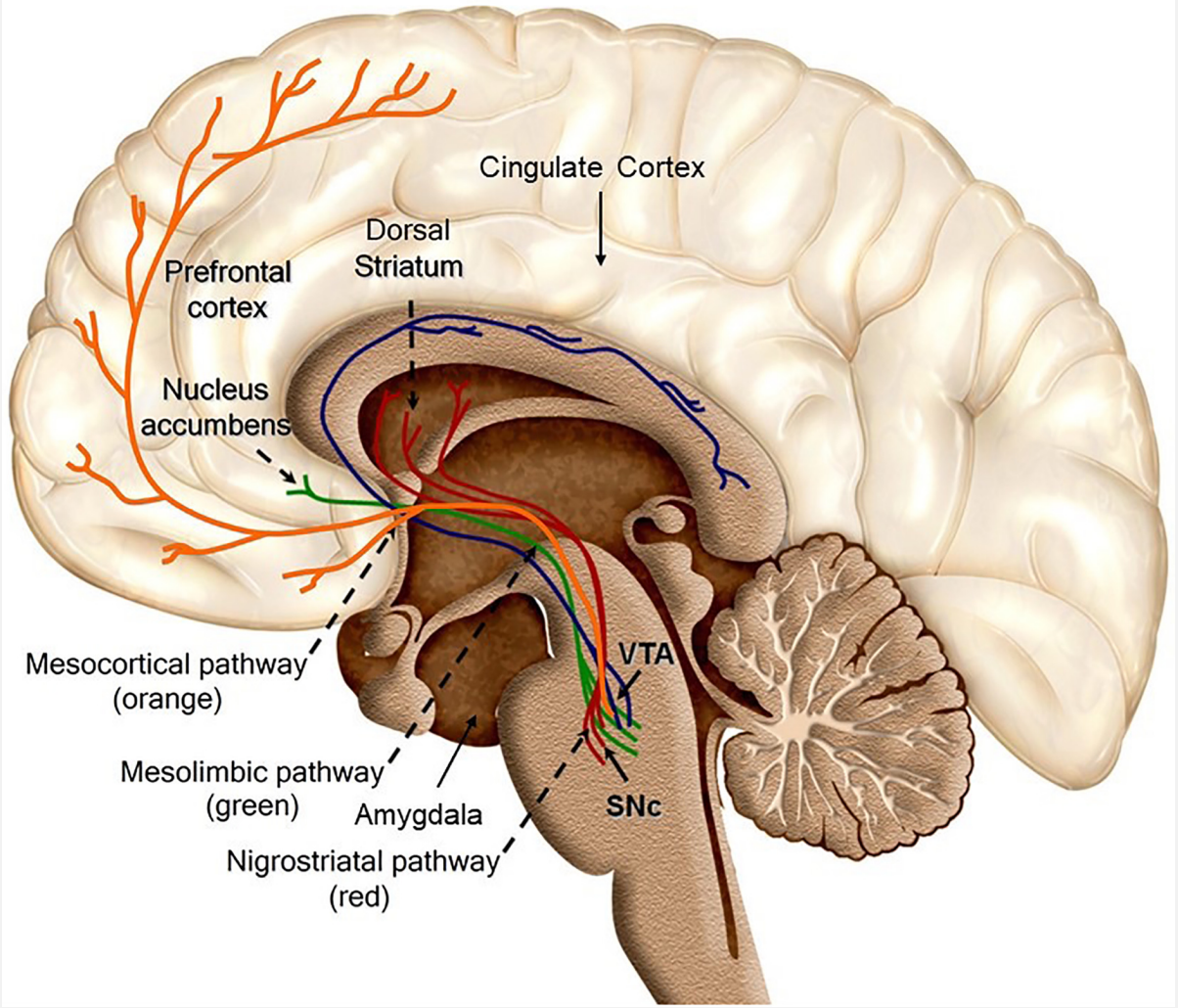
- Takes weeks to months to achieve full efficacy

- Suicide risk

Bui et al., 2022; Gang et al., 2021; Lathem et al., 2004; Prigerson et al., 2021

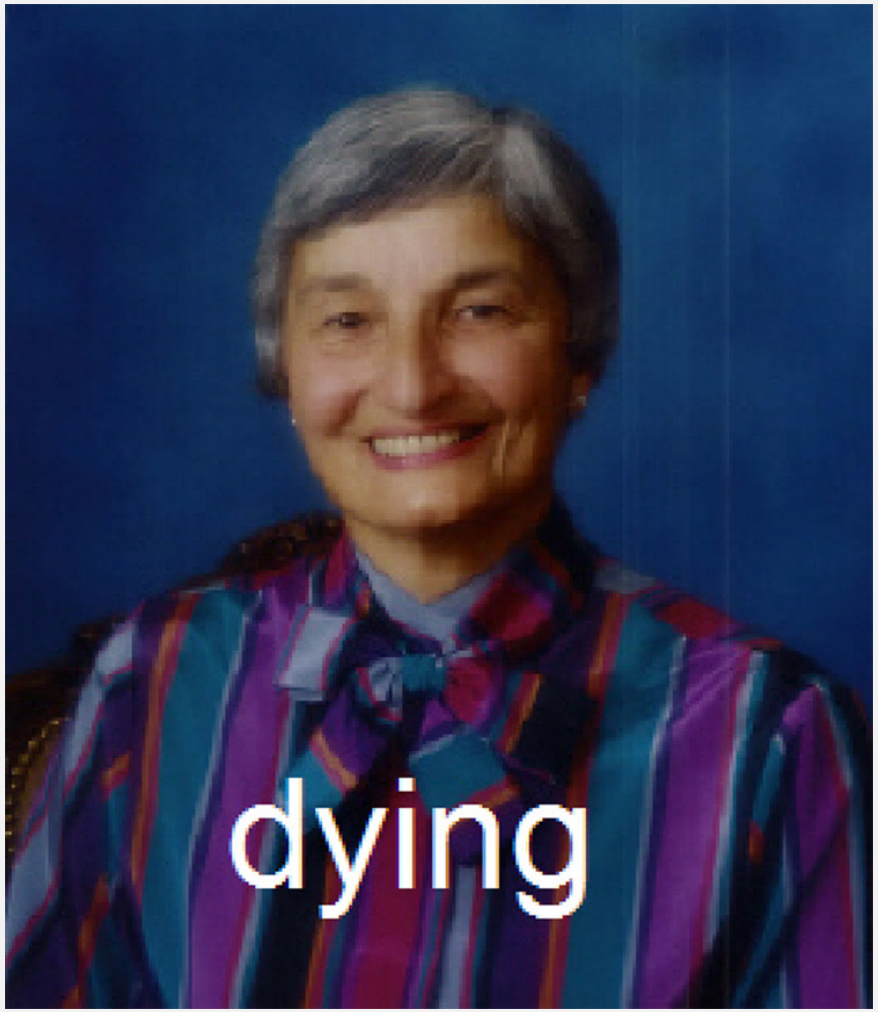
The Neurobiological Reward System

- Group of interconnected structures in the brain
- Uses dopamine as a signal to modulate the experience of reward
- Correlates between reward system and addiction



PGD as a Reward Dysfunction Disorder

- fMRI studies: PGD symptoms were associated with activity in the nucleus accumbens
- Bereaved persons crave a rewarding stimulus (the deceased)



Example of a picture-word composite (O'Connor et al., 2008)

Our Study:

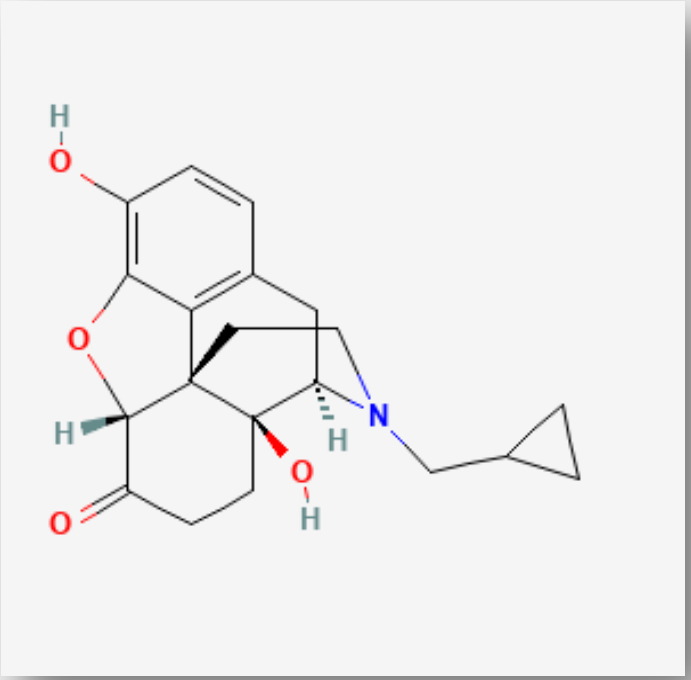
Naltrexone: A Possible Pharmacological Treatment for Prolonged Grief Disorder

Site MPI:
Yasin Ibrahim, MD
Jonathan Singer, PhD

Overall PI: Holly Prigerson, PhD

Naltrexone: An Opioid Antagonist

Why Naltrexone?



- **Targets the neurobiological reward system**
  - Endogenous Opioid Antagonist
  - Blocks rewarding effects of opioids and alcohol
  - Reduces opioid cravings
- **May reduce craving/yearning for the deceased**
- **Minimal side effects**
  - Includes nausea, vomiting, abdominal pain, headache, and fatigue
- **Accessibility**
  - Cost-effective ($25-$60 / month), often covered by insurance
  - Can be administered daily orally or monthly intramuscularly

Naltrexone Treatment for PGD: Aims

Primary Aim:

- To determine the efficacy of naltrexone (50mg daily for 8 weeks) in reducing PGD symptoms compared to placebo.

Secondary Aim:

- To evaluate the effects of naltrexone on social closeness with both the deceased (source of bereavement) and the living.

Exploratory Aims:

- To evaluate the effects of naltrexone on suicidal thoughts and behaviors.
- To evaluate the effects of naltrexone on health behaviors (e.g., alcohol and tobacco use, sleep, food consumption).

Recruitment

Clinical and community settings (e.g., Facebook ads, Newspaper ads, Primary Care Physician Referrals)

Eligibility Criteria

- ❖ Meets Diagnostic Criteria for PGD (assessed by clinical psychologist or psychiatrist)

Exclusion Criteria

- Currently pregnant or planning to become pregnant during study period
- Recently starting psychiatric medications or psychotherapy (less than 3 months ago)
- Serious suicidal intent with or without a plan through the C-SSRS
- Use of medications that may interact with Naltrexone to cause liver damage
- Active hepatitis or liver disease
- Elevated ALT or AST levels (higher than 1 SD above normal; measured via liver panel)

Study Design
Naltrexone Treatment for PGD

NCT0454
7985

Baseline Assessments

- Clinical interview (SCIP)
- PG-13-R
- Liver Function Test
- C-SSRS

Eligibility

- Meets criteria or sub-criterion threshold (Pg-13-R = 30+) for PGD
- No new psychiatric medication or psychotherapy
- ALT and AST levels < 1 SD above the upper limit of normal on initial laboratory examination
- No medications that interact with Naltrexone to cause liver damage

Randomization

- Oral Naltrexone: daily for 8 weeks
- Oral placebo: daily for 8 weeks

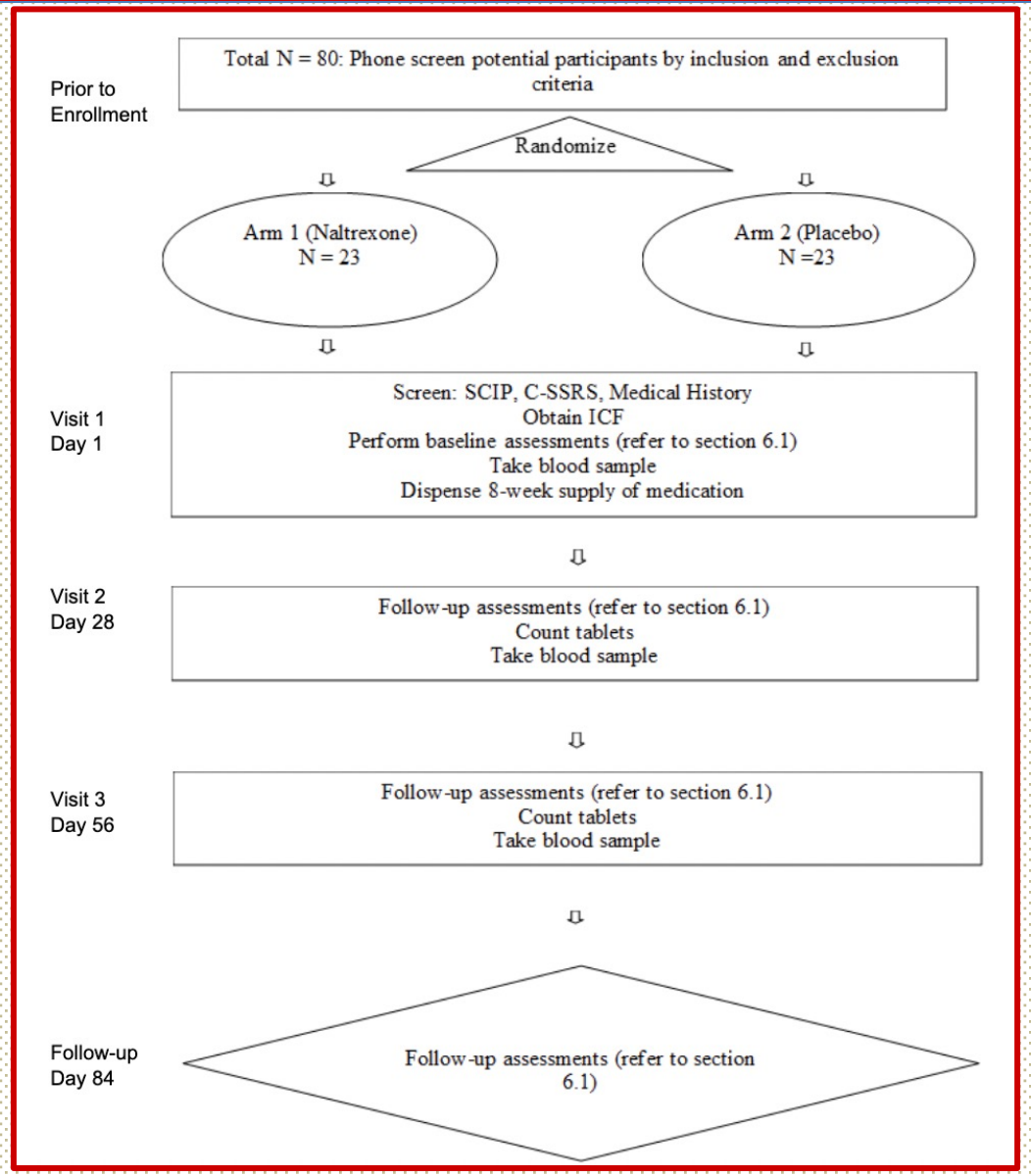
Termination

- Same evaluations provided at baseline are given again

Visits

- 4 weeks
- 8 weeks
- 12 weeks

Study Design



Blinding

Triple Blind Randomization

All participants, research staff, healthcare providers and statisticians blinded to the type of intervention the participant receives

Discontinuation/Withdrawal Criteria

Discontinuation or withdrawal due to suicidal ideation:

- Endorsing suicidal ideation post-visit 1 without intent or plan: will be called by the MPI to assess risk and severity (will still be able to participate in the study)

- Participants who express intent will be given appropriate supports by the MPI before withdrawal from the study intervention

Baseline (Visit 1) Measures

3.5.1 Visit 1 (baseline; Day 1)

- SCIP
- C-SSRS
- Medical History
- ICF
- Sociodemographics
- Review of Medications
- IOS Scale
- Social Integration Questionnaire
- Interpersonal Support Evaluation List
- Social Connectedness Survey
- Health Behaviors Survey
- Blood sample (LFTs, b-HCG)
- Dispense medication (8-week supply of 56 tablets)
- PCL-S
- PHQ-9

Weekly Measures (Weeks 1-12)

Prolonged Grief Scale-R (PG-13-R)
Posttraumatic Stress Disorder Checklist for DSM-IV (PCL-S)
Patient Health Questionnaire 9 (PHQ-9)
Adverse Event Evaluation

Study Design
Naltrexone Treatment for PGD

NCT04547985

Baseline Assessments
- Clinical interview (SCIP)
- PG-13-R
- Liver Function Test
- C-SSRS

Eligibility
- Meets criteria or sub-criterion threshold (Pg-13-R = 30+) for PGD
- No new psychiatric medication or psychotherapy
- ALT and AST levels < 1 SD above the upper limit of normal on initial laboratory examination
- No medications that interact with Naltrexone to cause liver damage

fMRI (Grief Elicitation Task; ecStroop)

Randomization

Oral Naltrexone: daily for 8 weeks

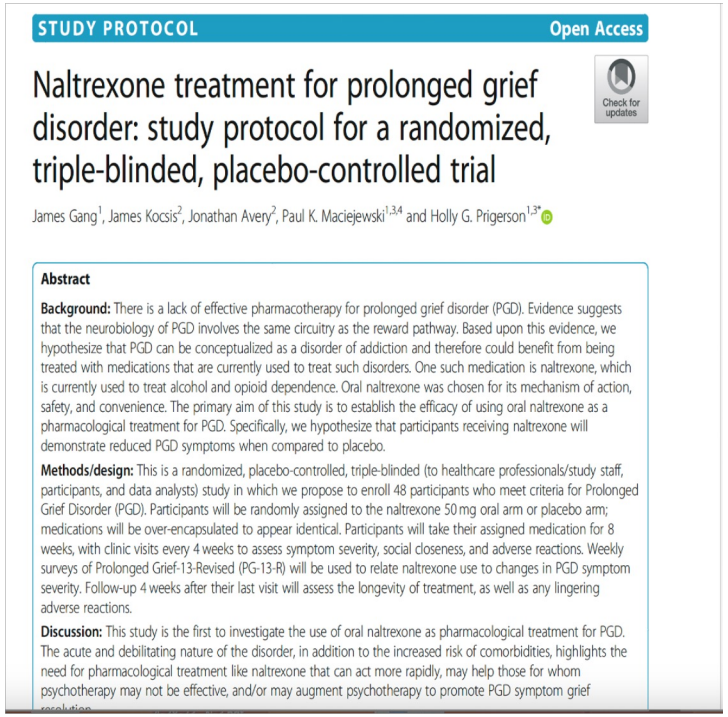
Oral placebo: daily for 8 weeks

Termination
- Same evaluations provided at baseline are given again

fMRI (Grief Elicitation Task; ecStroop)

Visits
- 4 weeks
- 8 weeks
- 12 weeks

The PGD Debate



STUDY PROTOCOL Open Access

Naltrexone treatment for prolonged grief disorder: study protocol for a randomized, triple-blinded, placebo-controlled trial

James Gang[1], James Kocsis[2], Jonathan Avery[2], Paul K. Maciejewski[1,3,4] and Holly G. Prigerson[1,3*]

Abstract

Background: There is a lack of effective pharmacotherapy for prolonged grief disorder (PGD). Evidence suggests that the neurobiology of PGD involves the same circuitry as the reward pathway. Based upon this evidence, we hypothesize that PGD can be conceptualized as a disorder of addiction and therefore could benefit from being treated with medications that are currently used to treat such disorders. One such medication is naltrexone, which is currently used to treat alcohol and opioid dependence. Oral naltrexone was chosen for its mechanism of action, safety, and convenience. The primary aim of this study is to establish the efficacy of using oral naltrexone as a pharmacological treatment for PGD. Specifically, we hypothesize that participants receiving naltrexone will demonstrate reduced PGD symptoms when compared to placebo.

Methods/design: This is a randomized, placebo-controlled, triple-blinded (to healthcare professionals/study staff, participants, and data analysts) study in which we propose to enroll 48 participants who meet criteria for Prolonged Grief Disorder (PGD). Participants will be randomly assigned to the naltrexone 50 mg oral arm or placebo arm; medications will be over-encapsulated to appear identical. Participants will take their assigned medication for 8 weeks, with clinic visits every 4 weeks to assess symptom severity, social closeness, and adverse reactions. Weekly surveys of Prolonged Grief-13-Revised (PG-13-R) will be used to relate naltrexone use to changes in PGD symptom severity. Follow-up 4 weeks after their last visit will assess the longevity of treatment, as well as any lingering adverse reactions.

Discussion: This study is the first to investigate the use of oral naltrexone as pharmacological treatment for PGD. The acute and debilitating nature of the disorder, in addition to the increased risk of comorbidities, highlights the need for pharmacological treatment like naltrexone that can act more rapidly, may help those for whom psychotherapy may not be effective, and/or may augment psychotherapy to promote PGD symptom grief

Article

Impairing Social Connectedness: The Dangers of Treating Grief With Naltrexone

Journal of Humanistic Psychology
2023, Vol. 63(3) 267–275

DOI: 10.1177/00221678221093822
journals.sagepub.com/home/jhp
SAGE

Kara Thieleman[1], Joanne Cacciatore[2], and Shanéa Thomas[3]

Abstract

A study is currently underway in the United States using the opioid antagonist naltrexone to treat prolonged grief, which is conceptualized in the study's proposal as an addiction disorder. The researchers' stated intention is to use the pharmaceutical agent to disrupt the griever's capacity to engage in social bonding to eliminate craving for the person who died. We believe this approach is misguided for a number of reasons. It demeans the importance of the relationship between the bereaved and the deceased loved one, further isolates grievers from the very social support networks that could help facilitate adaptation to bereavement, and could have a disproportionate negative impact on marginalized communities, who tend to rely more heavily on informal sources of support. We argue that social connection is at the very core of healing and that disregarding and interfering with this capacity could have widespread detrimental effects on grievers.

Keywords

grief, bereavement, social connection, naltrexone

Viewpoint

ANZJP

Prolonged grief disorder in *ICD*-11 and *DSM*-5-TR: Challenges and controversies

Australian & New Zealand Journal of Psychiatry
2023, Vol. 57(7) 944–951
DOI: 10.1177/00048674231154206

Maarten C Eisma

Abstract

Prolonged grief disorder has recently been added to the *International Classification of Diseases*, 11th edition and the *Diagnostic and Statistical Manual of Mental Disorders* 5, Text Revision. This historical development is often presented as a linear process culminating in the inclusion of valid, clinically relevant prolonged grief disorder criteria in diagnostic handbooks. The present contribution provides an overview of work contradicting this dominant narrative. First, I show that the developmental history of prolonged grief disorder has been nonlinear and that this yields questions on generalizability and problems with measurement of the newest criteria sets. Second, I highlight an important gap in the validity evidence: the distinction of prolonged grief disorder from normal grief. Third, I discuss concerns relating to the societal effects of the inclusion of prolonged grief disorder in diagnostic handbooks, including the medicalization of grief, development and adverse effects of pharmacotherapy and stigmatization. A more realistic, balanced view on the history, validity and societal impact of prolonged grief disorder appears appropriate. I recommend stringent validation of assessment instruments for prolonged grief disorder, convergence of criteria-sets, closing gaps in validity evidence and developing strategies to mitigate the negative effects of grief diagnoses.

Cons-Testing Naltrexone

- May isolate person grieving from social supports (e.g., family members and relationship partners) who are helpful in facilitating grief processes
  - Social isolation can lead to worse PGD outcomes
  - Particular concern for minority communities (e.g., Latine) that utilize social supports more
- Pharmacologic disruption of essential social ties within nondominant groups may further diminish trust of the medical community by those with a strong reliance on community care for their survival, healing, and wellness
- Comparisons between addiction and grief not well-supported outside of fMRI studies
- Psychologization of society and the emergence of "diagnostic cultures"
  - Human existence is being reduced to medical diagnostics
- Psychiatry/Psychology is "pushing pills" that will make a mourner forget the deceased loved one and result in social disconnection

Thieleman et al., 2023

Pros-Testing Naltrexone

- Reducing yearning for the deceased loved one might increase ability for bereaved individual to be reinforced by others/other aspects of their life
- Targets neurobiological reward system
- Well-tolerated medication
- Short half-life (between 4-13 hours)
- May be more effective than current alternatives and might be coupled with current psychological therapies
- Increase access to treatment
- Ability to test in combination with current psychological treatments
- Therapy might not work for everyone

Gang et al., 2021; Eisma et al., 2023; Khosravi & Kasaeiyan, 2023